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Adrenal insufficiency should be excluded before thyroxine replacement is started

EDITOR,—We strongly agree with C M Brosnan and N F C Gowing's comment that Addison's disease remains the unforgiving master of non-specificity and disguise.[1] We report two cases of Addison's disease in which the finding of a raised thyroid stimulating hormone concentration during investigations of weight loss prompted inappropriate treatment with thyroxine and precipitated an addisonian crisis.

Case 1—A 58 year old woman presented to her general practitioner with persistent nausea, vomiting, and weight loss. Thyroxine was started when investigations showed a thyroid stimulating hormone concentration of 27 mU/l (normal 0.3-5.0). Her condition deteriorated considerably, with abdominal pain and vomiting necessitating emergency admission. On examination she was dehydrated and shocked. Abdominal examination was unremarkable. Investigations showed a low thyroid stimulating hormone concentration (<0.05 mU/l) and a high total thyroxine concentration of 251 nmol/l (65-150). An abdominal ultrasound scan and results of upper gastrointestinal endoscopy were normal. She was noted to be pigmented. A short tetracosactrin test was performed, and intravenous hydrocortisone was started. Her improvement was dramatic, with resolution of all the symptoms. A positive result of the short tetracosactrin test, raised adrenocorticotrophic hormone concentration, and presence of adrenal antibodies confirmed autoimmune Addison's disease. Results of thyroid function tests remained normal after thyroxine was withdrawn.

Case 2—A 39 year old woman was admitted direct from the outpatient department, having been referred for investigation of weight loss, increasing weakness, and epigastric discomfort. Four weeks before her admission thyroxine replacement had been started because her thyroid stimulating hormone concentration was raised. On examination she was unwell and shocked, but otherwise the examination was unremarkable. Investigations showed a low sodium and a high potassium concentration. Withdrawal of thyroxine and replacement with hydrocortisone resulted in a dramatic resolution of her symptoms, as in case 1. Investigations confirmed autoimmune Addison's disease. Results of thyroid function tests remained normal.

The association of autoimmune thyroid and adrenal disease is well recognised and described.[2] Addisonian crisis precipitated by thyroxine replacement in patients with hypothyroidism has been documented.[3] To avoid precipitating a potentially fatal addisonian crisis in patients with hypothyroidism it is important to exclude adrenal insufficiency before starting thyroxine replacement treatment. In many patients with adrenal insufficiency abnormal blood thyroid variables return to normal after treatment with corticosteroids.[4]

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Hydrocortisone should be started immediately adrenal insufficiency is considered

EDITOR,—The most important lesson to be learnt from the cases of Addison's disease reported by C M Brosnan and N F C Gowing is not stated.[1] In any patient in whom addisonian crisis is suspected, serum should be saved for measurement of cortisol and adrenocorticotrophic hormone concentrations and treatment with intravenous hydrocortisone 100 mg should be started immediately. This should then be continued four hourly. The search for the precipitating cause can be concurrent.

Case 1 in Brosnan and Gowing's paper is a fairly classic case, and the biochemical abnormalities are suggestive of adrenal insufficiency. The authors state that the diagnosis of Addison's disease was considered, yet no treatment was started. I would hope that the lesson of the week is that, having considered the possibility of adrenal insufficiency, despite its non-specific presentation, you should treat it. Failure to do so has rapidly lethal results, as the case shows.

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N of 1 trials

Research is needed into why such trials are not more widely used

EDITOR,—Ten years after n of 1 trials were discovered for medicine by clinical epidemiologists from McMaster University,[1 2] Jeffrey Mahon and colleagues' study on theophylline for irreversible chronic airflow limitation merits several comments.[3] The authors cautiously state that further studies are needed before widespread use of n of 1 trials can be advocated in routine clinical practice. In 1986 we also wondered what the relevance of the contributions of this design to patients' care would be.[4] In view of the progress achieved since then we now hope that greater attention will be given to reasons why these designs are not more widely used despite their suitability to many problems.[3]

N of 1 trials have much in common with the classic crossover clinical trial.[4] In particular, both types of trials are subject to two sources of bias, sometimes referred to as treatment-period interaction. These sources of bias are, firstly, carryover effects (pharmacological effects persist in the second period) and, secondly, period effects (responses in the second period differ substantially from those in the first period, possibly owing to saturation of some biological response, fluctuations in the severity of disease, patients responding differently because of the "practice" in the first period, or other changes in environmental circumstances). In classic crossover studies, tests for carryover and period effects should routinely be conducted in the early stages of the analysis.[4] We thus wonder why tests for treatment-period interaction are not more common in n of 1 trials.

A given set of n of 1 trials will also share several intriguing features with another design, the recently developed case crossover study, which seems particularly appropriate for studying transient effects on the risk of acute events.[5] Might some of the analytical strategies proposed for the case crossover design be applicable to a study of n of 1 trials such as the one by Mahon and colleagues? We believe that most such studies of trials could benefit from methodological cross fertilisation—that is, from developments achieved both before and after the advent of n of 1 trials.

Beyond methodological matters, several issues that are clinically relevant warrant further scrutiny. One concerns the nature of the inferences made possible by the three types of studies (for example, on the therapeutic effectiveness of a given drug in groups of patients versus the clinical value of the drug in an individual patient). Surely other issues lie ahead.

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Placebos should be abandoned

EDITOR,—Jeffrey Mahon and colleagues report that n of 1 trials led to less use of theophylline without adverse effects on exercise capacity or quality of life in patients with irreversible chronic airflow limitation in a tertiary centre.[1] This finding is valuable but highly specific and does not justify the larger trial that the authors advocate to confirm the result. As the authors go some way to acknowledging, there are many other diseases, settings, groups of doctors and patients, forms of treatment, periods of follow up, and outcome measures that could be studied, and the results are not generalisable. Moreover, although the authors claim that "the decision about theophylline in the n of 1 trial group was usually governed by an objective, statistical result," among 18 paired treatment periods the difference in symptom scores was conclusive in only eight, and among four subjects in whom theophylline was continued the 95% confidence interval for the difference in diary scores excluded zero in only one.

A more useful approach would be to improve the ways in which we influence and assess response to treatment. There are good arguments for discarding the placebo since its effect cannot be clearly distinguished from that of either specific treatments[2] or a range of therapeutic skills.[3] Discarding the placebo would make it possible to increase patients' involvement in medical decision making, which itself can lead to improved outcomes.[4] At the very